

116-043

UNITED STATES PATENT APPLICATION OF

5

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for

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TREATMENT OF WARTS WITH TELLURIUM COMPOUNDS

20

BACKGROUND OF THE INVENTION:

5 Field of the Invention

This invention relates to the treatment of various warts.

10 Description of the Related Art

In U.S. 4,752,614, which is incorporated by reference, the use of certain tellurium compounds as anti-viral agents in plants or animals is disclosed. The virus that is exemplified is West Nile Virus. There is no known disclosure
15 in the prior art of the use of tellurium compounds for the treatment of viral infections in humans.

Verrucae or warts as verrucae are commonly known, are generally defined as a contagious, epithelial tumor caused by at least 35 different types of human papilloma virus
20 (HPV). Viral warts have been diagnosed in patients without regard to age or sex. The incidence of warts is most common in older children and is least common in persons of advanced age. Warts most often occur on the skin but may occur at any location in the body and may spread by auto-inneculation. In
25 some cases complete regression occurs after several months with or without treatment with recurrence at the same or at different locations. The types of warts include common (verruca vulgaris, plantar, palmar and periungal); flat; genital (Condylomata acuminata); butcher's; malignant
30 epidermodysplasia verruciformis; mepidermodysplasia verruciformis; cutaneous warts in immunosuppressed patients; laryngeal papillomas; and oral papilloma. Each of these conditions has been linked to specific types or groups of papilloma viruses. Various topical and/or surgical
35 techniques have been used for treating warts but no method

of treatment has been consistently effective. Surgical treatments have resulted in discomfort, prolonged healing and the formation of scars and/or keloids to a greater or lesser extent. Accordingly, a need exists for an improved
5 method of treating warts.

SUMMARY OF THE INVENTION:

The subject invention pertains to a method for
10 treatment of warts which comprises the administration of an effective amount of a tellurium compound to one who is afflicted with warts. The method of treatment includes the topical and systemic administration of a tellurium compound

Accordingly, it is a primary object of the invention
15 to provide a method for the treatment of warts which comprises the topical application of an effective amount of a tellurium compound to a wart.

It is also an object of this invention to provide a method for the treatment of warts which comprises the
20 systemic administration of an effective amount of a tellurium compound to an afflicted patient.

It is also an object of this invention to provide a method for the treatment of warts which avoids the scarring
25 and prolonged healing that accompanies surgical removal of warts.

These and other objects of the invention will become apparent from a review of the specification.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a photograph prior to treatment of a patient afflicted with condyloma warts.

Fig. 2 is a photograph after about two weeks of treatment as described in Example 1.

Fig. 3 is a photograph after about four weeks of treatment as described in Example 1.

Fig. 4 is a photograph after about six weeks of treatment as described in Example 1.

Fig. 5 is a photograph after about eight weeks of treatment as described in Example 1.

Fig. 6 is a photograph of the treatment of a verucca wart as described in Example 2 at the beginning of treatment.

Fig. 7 is a photograph after about two weeks of treatment as described in Example 2.

Fig. 8 is a photograph after about four weeks of treatment as described in Example 2.

Fig. 9 is a photograph of the treatment of verucca warts as described in Example 3 at the beginning of treatment.

Fig. 10 is a photograph after about two weeks of treatment as described in Example 3.

Fig. 10 is a photograph after about two weeks of treatment as described in Example 3.

Fig. 11 is a photograph after about four weeks of treatment as described in Example 3.

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DETAILED DESCRIPTION OF THE INVENTION:

The tellurium compounds for use in the invention include those of the formula:

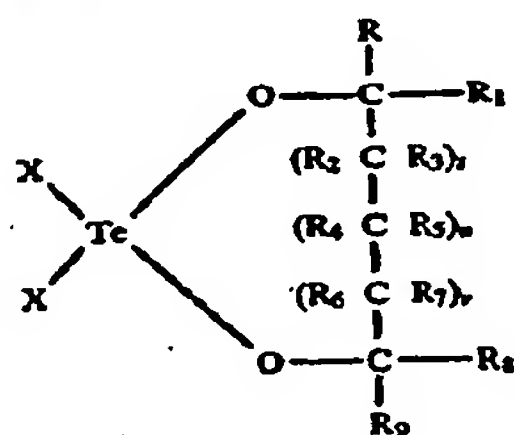
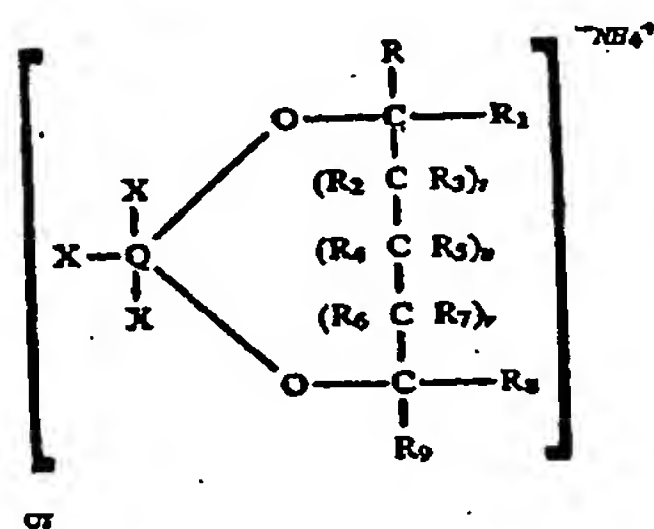
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or

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TeO₂ or complexes of TeO₂
(C)

or

5

PhTeCl₃,

(D)

or

5

TeX₄, when X is Cl, Br or F

or the following complex: TeO₂.HOCH₂CH₂OH.NH₄Cl;

10 or

(C₆H₅)₄P⁺(TeCl₃(O₂C₂H₄)) -

(E)

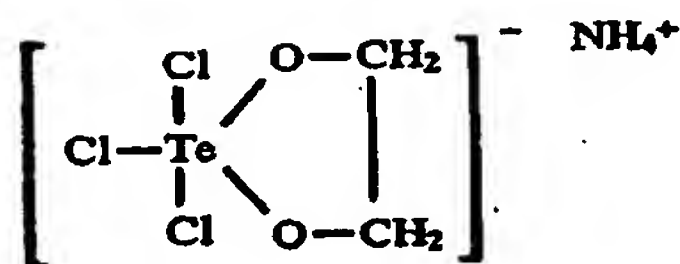
wherein t is 1 or 0; u is 1 or 0; v is 1 or 0; R, R₁, R₂, R₃,
R₄, R₅, R₆, R₇, R₈, and R₉ are the same or different and are
independently selected from the group consisting of hydrogen,
15 hydroxyalkyl of 1 to 5 carbons, hydroxy, alkyl or from 1 to 5
carbon atoms, halogen, haloalkyl of 1 to 5 carbon atoms,
carboxy, alkylcarbonylalkyl of 2 to 10 carbons, alkanoyloxy
of 1 to 5 carbon atoms, carboxyalkyl of 1 to 5 carbons atoms,
acyl, amido, cyano, amidoalkyl of 1 to 5 carbons, N-
20 monoalkylamidoalkyl of 2 to 10 carbons, N,N-dialkylamidoalkyl
of 4 to 10 carbons, cyanoalkyl of 1 to 5 carbons alkoxy of 1
to 5 carbon atoms, alkoxyalkyl of 2 to 10 carbon atoms and -
COR₁₀ wherein R₁₀ is alkyl of 1 to 5 carbons; and X is halogen;
while the ammonium salt is illustrated, it is understood that
25 other pharmaceutically acceptable salts such as K⁺ are within
the scope of the invention. The compounds with the five
membered rings are preferred.

As used herein and in the appended claims, the term
alkyl of 1 to 5 carbon atoms includes straight and branched
30 chain alkyl groups such as methyl; ethyl; n-propyl; n-butyl,
and the like; the term hydroxyalkyl of 1 to 5 carbon atoms
includes hydroxymethyl; hydroxyethyl; hydroxy-n-butyl; the
term haloalkyl of 1 to 5 carbon atoms includes chloromethyl;
2-iodoethyl; 4-bromo-n-butyl; iodoethyl; 4-bromo-n-pentyl and
35 the like; the term alkanoyloxy of 1 to 5 carbon atoms

includes acetyl, propionyl, butanoyl and the like; the term carboxyalkyl includes carboxymethyl, carboxyethyl, ethylenecarboxy and the like; the term alkylcarbonylalkyl includes methanoylmethyl, ethanoylethyl and the like; the term amidoalkyl includes $-\text{CH}_2\text{CONH}_2$; $-\text{CH}_2\text{CH}_2\text{CONH}_2$; $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CONH}_2$ and the like; the term cyanoalkyl includes $-\text{CH}_2\text{CN}$; $-\text{CH}_2\text{CH}_2\text{CN}$; $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CN}$ and the like; the alkoxy, of 1 to 5 carbon atoms includes methoxy, ethoxy, n-propoxy, n-pentoxy and the like; the terms halo and halogen are used to signify chloro, bromo, iodo and fluoro; the term acyl includes R_{16}CO wherein R_{16} is H or alkyl of 1 to 5 carbons such as methanoyl, ethanoyl and the like; the term aryl includes phenyl, alkylphenyl and naphthyl; the term N-monoalkylamidoalkyl includes $-\text{CH}_2\text{CH}_2\text{CONHCH}_3$, $-\text{CH}_2\text{CONHCH}_2\text{CH}_3$; the term N,N-dialkylamidoalkyl includes $-\text{CH}_2\text{CON}(\text{CH}_3)_2$; $\text{CH}_2\text{CH}_2\text{CON}(\text{CH}_2\text{-CH}_3)_2$. The tellurium based compounds that are preferred include those of the formula:

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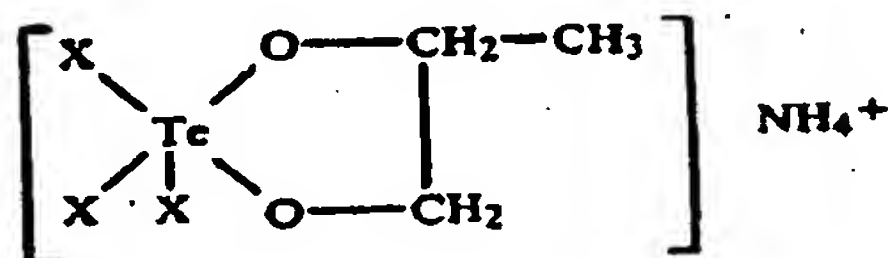
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and

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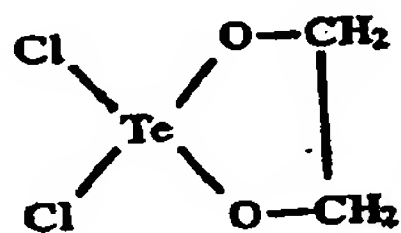


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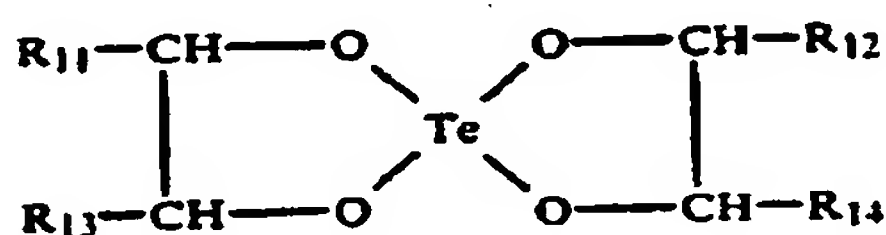
wherein X is halogen. The preferred halogen species is

chloro.

Other compounds which are based on tellurium and may be used in the practice of the invention include PhTeCl_3 , TeO_2 and TeX_4 (C_6H_5)₄, $\text{P}^+ (\text{TeCl}_3(\text{O}_2\text{C}_2\text{H}_4))^-$ (Z. Naturforsch, 36, 307-312 (1981)). Compounds of the following structure are also included:



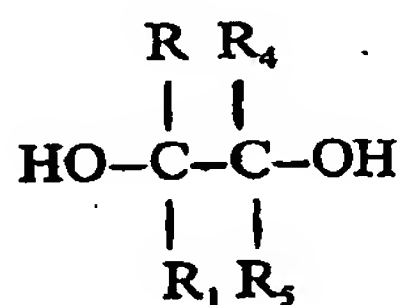
Other compounds useful for the practice of invention include:



wherein R_{11} , R_{12} , R_{13} and R_{14} are independently selected from the group consisting of hydrogen, hydroxy-alkyl of 1-5 carbons atoms, hydroxy and alkyl of 1-5 carbons atoms.

Useful dihydroxy compounds for use in the preparation of compounds of structure A or B, include those of formula I wherein R , R_1 , R_4 and R_5 are as shown in the Table:

TABLE



(I)

40

R

R_1

R_4

R_5

H

H

H

H

	H	Cl	H	H
	H	OCH ₃	H	H
	H	COOCH ₃	H	H
	H	H	CN	H
5	H	CHO	H	H
	H	H	COOH	H
	H	CH ₂ COOH	H	H
	H	H	CH ₂ COOCH ₃	H
	H	I	H	H
10	H	H	Br	H
	H	H	CONH ₂	H
	H	H	CH ₂ OH	H
	H	COOH	H	H

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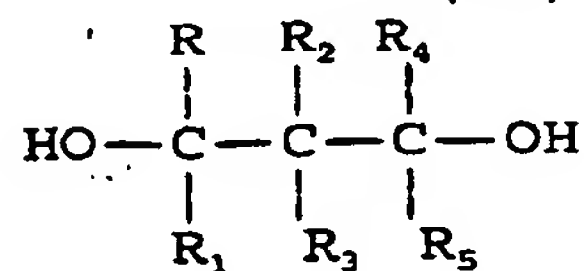
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Other dihydroxy compounds for use in the preparation of compounds A and B include those of formula II wherein R, R₁, R₂, R₃, R₄ and R₅ are as shown in the Table:

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(II)



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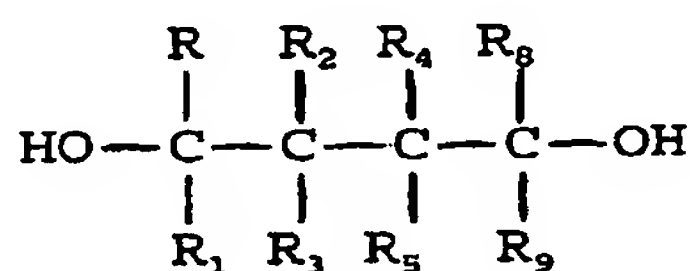
	R	R ₁	R ₂	R ₃	R ₄	R ₅
15	H	H	H	H	H	H
	H	H	Cl	H	H	H
	H	CH ₂ OH	H	H	H	H
	H	H	OH	H	H	H
	H	H	H	CH ₃	H	H
20	H	H	H	CH ₂ Cl	H	H
	H	H	H	COOH	H	H
	H	H	H	CH ₂ COOH	H	H
	H	H	H	CHO	H	H
	H	H	H	H	H	CH ₂ CHO
25	H	H	CONH ₂	H	H ₂	CH ₃
	H	H	H	CN	H	H
	H	H	H	H	CH ₂ COHN ₂	H
	H	H	H	COOCH ₃	H ₃	H
	H	H ₃	OCH ₃	H	H	H
30						

Other dihydroxy compounds for use in making compound of formula A and B include those of formula III wherein R, R₁, R₂, R₃, R₄ and R₅ are as shown in the Table.

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(III)

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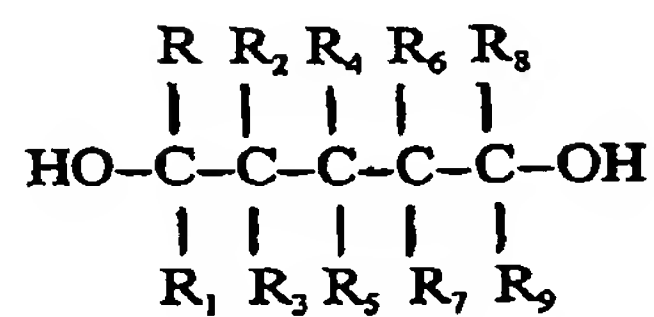
R	R ₁	R ₂	R ₃	R ₄	R ₅	R ₈	R ₉
H	H	H	H	H	H	H	H
H	H	Cl	H	H	H	H	H
H	H	H	H	Br	H	H	H
H	H	OCH ₃	H	H	H	H	H
H	H	CONH ₂	H	H	H	H	H
H	Br	H	H	H	H	H	H
H	H	H	H	CH ₂ COOH	H	H	H
H	H	Cl	Cl	H	H	H	H
H	CH ₂ COOH	H	H	H	H	H	H
H	H	CH ₃	H	H	H	H	H
H	CH ₃	H	H	H	H	H	H
H	CH ₂ Cl	H	H	H	H	H	H
H	H	H	I	H	H	H	H
H	CH ₂ CN	H	H	H	H	H	H
H	H	H	H	CH ₂ CH ₂ OH	H	H	H

Additional dihydroxy compounds include those of formula IV wherein R, R₁, R₂, R₃, R₄ and R₅ are as shown in the Table.

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(IV)



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R	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	R ₇	R ₈	R ₉
—									
H	H	H	H	H	H	H	H	H	H
H	H	Cl	H	H	H	Cl	H	H	H
H	H	Cl	Cl	H	H	H	H	H	H
H	H	CONCH ₃	H	H	H	Br	H	H	H
H	H	Br	H	H	H	CON(CH ₃) ₂	H	H	H
H	H	H	OCH ₃	H	H	H	H	H	H
H	H	H	H	OCH ₃	H	H	H	H	H
H	H	H	H	CH ₂ COOH	H	H	H	H	H
H	H	COOH	H	H	H	H	H	H	H
H	CH ₃	H	H	H	H	H	H	H	H
CH ₃	H	H	H	H	CH ₃	H	H	H	H
H	CH ₂ CH ₃	H	H	H	H	H	Cl	H	H
H	CH ₂ CN	H	H	CH ₂ OH	H	H	H	H	H
H	H	H	I	H	H	H	H	CN	H
H	CH ₂ CH ₂ COOH	H	H	H	H	H	H	H	H
H	H	CHO	H	H	H	H	H	H	H
H	H	H	F	H	H	H	H	H	H

Compounds of the following formula are also included:



herein R_{15} , R_{16} , R_{17} , and R_{18} are independently selected from halogen, alkyl of 1-5 carbons; aryl, acyl of 1-5 carbon
10 hydroxyalkyl of 1-5 carbons and aminoalkyl of 1-5 carbons may be made by reacting the appropriate di, tri or tetrahalotelluride with the appropriate hydroxy compound which may be of the formula: $HO-R_{19}$; wherein R_{19} is alkyl of 1 to 5 carbons, haloalkyl of 1 to 5 carbons, aryl, alkylaryl,
15 alkylamido of 1 to 5 carbons, alkylcarbonyl of 1 to 5 carbons, cyanoalkyl of 1 to 5 carbons, cyanoalkyl of 1 to 5 carbons, and an alkoxyalkyl of 2 to 10 carbons. Specific examples of R_{16} include methyl, ethyl, n-propyl, phenyl, tolyl, amidoethyl, cyanomethyl, methyloxymethyl and
20 CH_2CH_2COOH .

These compounds are described in United States Patent No. 4,761,490 which is incorporated by reference. In addition, $TeCl_4$, $TeBr_4$ and compounds which give in aqueous solution TeO_2 preferably in the form of a complex such as for
25 example TeO_2 complex with citric acid or ethylene glycol.

The preferred compound is ammonium trichloro (dioxoethylene-O,O') tellurate.

The topical treatment of warts involves contacting the
30 affected area with a liquid or semisolid composition of the tellurium compound in a liquid or semisolid vehicle. The liquid vehicle may comprise water, dimethyl sulfoxide, propylene glycol, ethanol and solvents containing polyhydroxy groups.

35 The semisolid vehicle may comprise a hydrophilic or a

hydrophobic ointment base such as petrolatum U.S.P., or water washable cream type base such as polyethylene glycol ointment U.S.P.

5 The concentration of the tellurium compound in the topical composition may vary from 1 to 40wt% and more preferably from 15 to 25wt.%. In selected cases where warts are found on cornified epithelial tissue, it may be desirable to coadminister a keratolytic agent such as salicylic acid at concentrations of 20 to 50wt% of the total
10 weight of the tellurium containing composition.

Systemic treatment may be achieved by oral or parenteral administration of the tellurium compound at a dose of 0.1 to 5.0 mg/kg of body weight, preferably 1 to 3mg/kg given daily in divided doses.

15 The preferred method of administration will be determined by the type of wart that is being treated and the location of the wart. The optimum dose and frequency may be determined by the individualized response to the clinical
20 treatment of particular cases.

EXAMPLE 1

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A human patient with *condyloma acuminatum* in the perianal region is treated with a dispersion of ammonium trichloro (dioxoethylene-O,O') tellurate that is prepared by dissolving
30 a sufficient amount of the tellurate compound in dimethyl sulfoxide to make a 40%w/w solution and then combining that solution with an equal weight of petrolatum, U.S.P. to make a 20%w/w dispersion of the tellurate. This formulation is topically applied twice daily to cover the affected area for
35 a period of about 4 weeks. After a few days the lesion

changes color from pink to grey-black and after about 4 to 5 weeks, the lesion sloughs off without leaving any scarring. Figs. 1-5 show the effect of the therapy on the condyloma at bi-weekly intervals during the period of treatment

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EXAMPLE 2

A human patient with a verrucca lesion on the hand is treated with the same dispersion of ammonium trichloro (dioxoethylene-O,O') tellurate that was prepared in Example 1. The formulation was applied twice daily for a period of about 4 weeks. After about four weeks the wart sloughs off and leaves no scar on the treated area. Figs. 6-8 show the progress of treatment at biweekly intervals.

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EXAMPLE 3

A human patient with multiple verrucca lesions on the hand is treated with the same dispersion of ammonium trichloro (dioxoethylene-O,O') tellurate that was prepared in Example 1. The formulation was applied twice daily for a period of about 4 weeks. After about four weeks the wart sloughs off and leaves no scar on the treated area. Figs. 9-11 show the progress of treatment at biweekly intervals.

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